The TLX-miR-219 cascade regulates neural stem cell proliferation in neurodevelopment and schizophrenia iPSC model.

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Public Summary:
Dysregulated expression of miR-219, a brain-specific microRNA, has been observed in neurodevelopmental disorders, such as schizophrenia (SCZ). However, its role in normal mammalian neural stem cells (NSCs) and in SCZ pathogenesis remains unknown. We show here that the nuclear receptor TLX, an essential regulator of NSC proliferation and self-renewal, inhibits miR-219 processing. miR-219 suppresses mouse NSC proliferation downstream of TLX. Moreover, we demonstrate upregulation of miR-219 and downregulation of TLX expression in NSCs derived from SCZ patient iPSCs and DISC1-mutant isogenic iPSCs. SCZ NSCs exhibit reduced cell proliferation. Overexpression of TLX or inhibition of miR-219 action rescues the proliferative defect in SCZ NSCs. Therefore, this study uncovers an important role for TLX and miR-219 in both normal neurodevelopment and in SCZ patient iPSC-derived NSCs. Moreover, this study reveals an unexpected role for TLX in regulating microRNA processing, independent of its well-characterized role in transcriptional regulation.

Scientific Abstract:
Dysregulated expression of miR-219, a brain-specific microRNA, has been observed in neurodevelopmental disorders, such as schizophrenia (SCZ). However, its role in normal mammalian neural stem cells (NSCs) and in SCZ pathogenesis remains unknown. We show here that the nuclear receptor TLX, an essential regulator of NSC proliferation and self-renewal, inhibits miR-219 processing. miR-219 suppresses mouse NSC proliferation downstream of TLX. Moreover, we demonstrate upregulation of miR-219 and downregulation of TLX expression in NSCs derived from SCZ patient iPSCs and DISC1-mutant isogenic iPSCs. SCZ NSCs exhibit reduced cell proliferation. Overexpression of TLX or inhibition of miR-219 action rescues the proliferative defect in SCZ NSCs. Therefore, this study uncovers an important role for TLX and miR-219 in both normal neurodevelopment and in SCZ patient iPSC-derived NSCs. Moreover, this study reveals an unexpected role for TLX in regulating microRNA processing, independent of its well-characterized role in transcriptional regulation.